Channel-facilitated membrane transport: Average lifetimes in the channel

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The transport of many solutes across biological membranes happens with the help of specialized proteins that form water-filled channels traversing the membranes. Recent experimental and theoretical work demonstrates that solute translocation can be facilitated by attractive interactions between the channel and penetrating particle. Here we consider an important aspect of channel-facilitated passive transport, the average lifetimes in the channel for those particles that traverse the channel and those that return, as well as the total average lifetime of the particle in the channel. Exact expressions for the average lifetimes are derived in the framework of a one-dimensional diffusion model. The validity of our one-dimensional analysis is verified by good agreement of the theoretical predictions with the average lifetimes found in three-dimensional Brownian dynamics simulations.
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I. INTRODUCTION

It is well documented now that membrane transport of metabolites and other solutes larger than monoatomic ions is assisted and regulated by specialized membrane proteins forming water-filled channels. The basic mechanisms of this channel-facilitated transport are interesting from both practical and conceptual points of view. As a specific example, we mention recent studies of antibiotic transport through bacterial channels[1,2] where progress in understanding of the permeation mechanism may lead to the development of more efficient drugs. Conceptually, although the constructive role of attractive interactions between permeating particles and the channel has been appreciated for many years,[3–5] a comprehensive theory capable of offering a clear understanding and a reliable quantitative description of channel-facilitated metabolite transport is still to be developed.

A particle that enters the channel either returns and escapes on the same side of the membrane where it enters or traverses the channel and escapes on the opposite side of the membrane. Key quantities that characterize this process are translocation and return probabilities and average lifetimes in the channel of translocating and returning particles, as well as the total average lifetime of the particle in the channel. These quantities are building blocks of the theory of the channel-facilitated transport.

General expressions for the translocation and return probabilities are found in our previous study.[6] In the present paper we derive expressions for the average lifetimes in the channel for translocating and returning particles, which will be called average return and translocation times, respectively. These lifetimes are conditional because they are calculated for the two subsets of all possible realizations of the random process. The total average lifetime of the particle in the channel is obtained as the weighted sum of the conditional lifetimes, in which the weight factors are the translocation and return probabilities derived in Ref. 6.

To illustrate some qualitative features of the average lifetimes predicted by the general theory, we study a special case in which a symmetric square-well potential occupies some part of the channel. We find that both the total average lifetime in the channel and the average return time are monotonically increasing functions of the well depth and length. Such a behavior agrees with general intuitive ideas. In contrast, the dependence of the average translocation time on the well length is somewhat counterintuitive. This time increases with the length when the length is small, reaches a maximum when the well occupies half of the channel, and then starts to decrease. Concerning the dependence on the well depth, the average translocation time monotonically increases with depth. The deeper the well, the more pronounced is turnover behavior of the translocation time.

Another surprising result is that the average translocation time does not depend on the direction in which the particle translocates. This statement is true for the arbitrary dependence of the particle potential energy in the channel, as shown in Fig. 1. Specifically, this includes the case of a finite difference in the potential energy between the channel ends,

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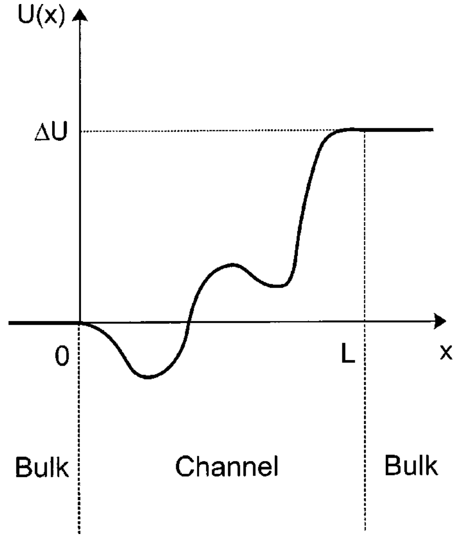

FIG. 1. Schematic view of the particle potential energy $U(x)$ in the membrane channel.

$\Delta U \neq 0$ in Fig. 1, where the particle has to go either up or down the energy gradient depending on the direction of the translocation.

The outline of the paper is as follows. After the model is formulated in the following section, we derive a general solutions in Sec. III. The case of the symmetric square-well potential is discussed in detail in Sec. IV. Three-dimensional Brownian dynamics simulations performed for this potential to test our one-dimensional theory are also reported in this section. The simulation results agree well with the theoretical predictions. Section V contains a brief summary and concluding remarks. In the Appendix we demonstrate that the translocation time does not depend on the direction of translocation in the framework of a simple two-site model of the channel.

II. MODEL AND DEFINITIONS

Consider a particle that enters a cylindrical membrane channel. The particle either traverses the channel or escapes on the same side of the membrane, where it has entered. Our goal is to calculate the average time that the particle spends in the channel in both cases as well as its total average lifetime in the channel.

Our derivation is based on an approximate treatment of the particle motion in the channel as one-dimensional diffusion along the channel axis. This model describes the interaction of the particle with the channel in terms of the potential of mean force $U(x)$, which acts on the particle at the point x (Fig. 1), and position-dependent diffusion coefficient $D(x)$. The propagator or Green function $G(x,t|x_0)$, which is the probability density to find the particle at point x at time t on condition that the particle was at x_0 at $t=0$, satisfies the diffusion (Smoluchowski) equation

$$\frac{\partial G}{\partial t} = \frac{\partial}{\partial x}\left\{ D(x) e^{-\beta U(x)} \frac{\partial}{\partial x}[G e^{\beta U(x)}] \right\}, \tag{2.1}$$

where $\beta = (k_B T)^{-1}$, and k_B and T are the Boltzmann constant and absolute temperature. The propagator satisfies the initial condition

$$G(x,0|x_0) = \delta(x - x_0). \tag{2.2}$$

Radiation boundary conditions imposed at the end points $x=0$, $x=L$ describe the escape of the particle from the channel:

$$\begin{aligned} \frac{\partial}{\partial x}[G e^{\beta U(x)}]\bigg|_{x=0} &= \frac{k_0}{D(0)} e^{\beta U(0)} G(0,t|x_0), \\ -\frac{\partial}{\partial x}[G e^{\beta U(x)}]\bigg|_{x=L} &= \frac{k_L}{D(L)} e^{\beta U(L)} G(L,t|x_0), \end{aligned} \tag{2.3}$$

where the rate constants k_0 and k_L characterize the efficiency of the escape. Two limiting cases of $k=\infty$ and $k=0$ correspond to perfectly absorbing and reflecting end points, respectively. In what follows $k_0, k_L \neq 0, \infty$ because there is no translocation in both cases.

Escape from the channel is described by the probability fluxes through the end points

$$f_0(t|x_0) = k_0 G(0,t|x_0), \quad f_L(t|x_0) = k_L G(L,t|x_0). \tag{2.4}$$

Their sum is the probability density for the lifetime in the channel of the particle initially at x_0:

$$\varphi(t|x_0) = f_0(t|x_0) + f_L(t|x_0). \tag{2.5}$$

The total probabilities of escape through the left and right end points, denoted by $P_0(x_0)$ and $P_L(x_0)$, are given by

$$P_0(x_0) = \int_0^\infty f_0(t|x_0)\,dt, \quad P_L(x_0) = \int_0^\infty f_L(t|x_0)\,dt. \tag{2.6}$$

One can see that

$$P_0(x_0) + P_L(x_0) = \int_0^\infty \varphi(t|x_0)\,dt = 1. \tag{2.7}$$

The probability densities for the lifetimes in the channel on condition that the particle, initially at x_0, escape through the end points at $x=0$ or $x=L$ are, respectively, defined by

$$\begin{aligned} \varphi_0(t|x_0) &= \frac{1}{P_0(x_0)} f_0(t|x_0), \\ \varphi_L(t|x_0) &= \frac{1}{P_L(x_0)} f_L(t|x_0). \end{aligned} \tag{2.8}$$

The conditional average lifetimes $\overline{t_0}(x_0)$ and $\overline{t_L}(x_0)$ are given by

$$\begin{aligned} \overline{t_0}(x_0) = \int_0^\infty t\varphi_0(t|x_0)\,dt &= \frac{1}{P_0(x_0)} \int_0^\infty t f_0(t|x_0)\,dt \\ &= \frac{k_0}{P_0(x_0)} \int_0^\infty t G(0,t|x_0)\,dt, \end{aligned}$$

$$\begin{aligned}\overline{t_L}(x_0)&=\int_0^\infty t\varphi_L(t|x_0)dt\\&=\frac{1}{P_L(x_0)}\int_0^\infty tf_L(t|x_0)dt\\&=\frac{k_L}{P_L(x_0)}\int_0^\infty tG(L,t|x_0)dt.\end{aligned}\tag{2.9}$$

Using the definitions in Eqs. (2.5) and (2.8), one can see that

$$\varphi(t|x_0)=\varphi_0(t|x_0)P_0(x_0)+\varphi_L(t|x_0)P_L(x_0).\tag{2.10}$$

As a consequence, the average particle lifetime in the channel is

$$\overline{t}(x_0)=\int_0^\infty t\varphi(t|x_0)dt=\overline{t_0}(x_0)P_0(x_0)+\overline{t_L}(x_0)P_L(x_0).\tag{2.11}$$

The average translocation and return times, which are the average lifetimes in the channel of translocating (*tr*) and returning (*r*) particles that enter the channel at $x_0=0$ and $x_0=L$, are denoted by $\overline{t_{tr}}(0)$, $\overline{t_r}(0)$, $\overline{t_{tr}}(L)$, and $\overline{t_r}(L)$, respectively. These times can be written in terms of the conditional average lifetimes $\overline{t_0}(x_0)$ and $\overline{t_L}(x_0)$ introduced in Eq. (2.9) as follows:

$$\begin{aligned}&\overline{t_{tr}}(0)=\overline{t_L}(0),\quad \overline{t_r}(0)=\overline{t_0}(0),\\&\overline{t_{tr}}(L)=\overline{t_0}(L),\quad \overline{t_r}(L)=\overline{t_L}(L).\end{aligned}\tag{2.12}$$

In what follows we derive expressions for $\overline{t_0}(x_0)$ and $\overline{t_L}(x_0)$. The relations in Eqs. (2.12) are then used to find the average return and translocation times.

The functions $P_0(x_0)$ and $P_L(x_0)$ give the probabilities of two possible outcomes of the stochastic process. They are called "splitting probabilities."[7–9] Associated conditional average lifetimes $\overline{t_0}(x_0)$ and $\overline{t_L}(x_0)$ are similar to, but not identical with, the conditional mean first-passage times discussed in detail by Redner in Ref. 9. The difference between these times lies in the boundary conditions at the ends of the interval. To find conditional mean first-passage times one has to impose absorbing boundary conditions. Conditional average lifetimes $\overline{t_0}(x_0)$ and $\overline{t_L}(x_0)$ will be derived for radiation boundary conditions. This difference in the boundary conditions is important because a diffusing particle cannot cross an absorbing boundary and, hence, cannot enter the channel.

III. SOLUTION

It is convenient to introduce the auxiliary times $\tau_0(x_0)$ and $\tau_L(x_0)$ defined by

$$\begin{aligned}\tau_0(x_0)&=\int_0^\infty tf_0(t|x_0)dt=k_0\int_0^\infty tG(0,t|x_0)dt,\\\tau_L(x_0)&=\int_0^\infty tf_L(t|x_0)dt=k_L\int_0^\infty tG(L,t|x_0)dt,\end{aligned}\tag{3.1}$$

which are functions of the particle initial position. These times satisfy the equation that can be derived from the backward equation for the propagator considered as a function of x_0:

$$\frac{\partial G}{\partial t}=e^{\beta U(x_0)}\frac{\partial}{\partial x_0}\left\{D(x_0)e^{-\beta U(x_0)}\frac{\partial G}{\partial x_0}\right\}.\tag{3.2}$$

The initial condition is given in Eq. (2.2), and the boundary conditions are

$$\begin{aligned}\left.\frac{\partial G}{\partial x_0}\right|_{x_0=0}&=\frac{k_0}{D(0)}G(x,t|0),\\-\left.\frac{\partial G}{\partial x_0}\right|_{x_0=L}&=\frac{k_L}{D(L)}G(x,t|L).\end{aligned}\tag{3.3}$$

Using Eqs. (3.1)–(3.3), one can check that $\tau_0(x_0)$ and $\tau_L(x_0)$ satisfy

$$e^{\beta U(x_0)}\frac{d}{dx_0}\left\{D(x_0)e^{-\beta U(x_0)}\frac{d\tau_{0,L}(x_0)}{dx_0}\right\}=-P_{0,L}(x_0),\tag{3.4}$$

with the boundary conditions

$$\begin{aligned}\left.\frac{d\tau_{0,L}(x_0)}{dx_0}\right|_{x_0=0}&=\frac{k_0}{D(0)}\tau_{0,L}(0),\\-\left.\frac{d\tau_{0,L}(x_0)}{dx_0}\right|_{x_0=L}&=\frac{k_L}{D(L)}\tau_{0,L}(L).\end{aligned}\tag{3.5}$$

The probabilities $P_0(x_0)$ and $P_L(x_0)$ are derived in Ref. 6 and are given by

$$\begin{aligned}P_0(x_0)&=\frac{k_0\left[1+k_Le^{-\beta\Delta U}\int_{x_0}^L\frac{e^{\beta U(y)}}{D(y)}dy\right]}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta u}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy},\\P_L(x_0)&=\frac{k_Le^{-\beta\Delta U}\left[1+k_0\int_0^{x_0}\frac{e^{\beta U(y)}}{D(y)}dy\right]}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy}.\end{aligned}\tag{3.6}$$

Here we have taken $U(0)=0$ and introduced the notation $\Delta U=U(L)$ for the difference in the potential energies at the channel ends (Fig. 1).

Solving Eq. (3.4), one can find $\tau_0(x_0)$ and $\tau_L(x_0)$ and eventually the average return and translocation times defined in Eq. (2.12). Surprisingly, we find that the average translocation times in both directions coincide. For this reason we have introduced a unified notation for the average translocation time, $\overline{t_{tr}}(0)=\overline{t_{tr}}(L)=\overline{t_{tr}}$. It is given by

$$\overline{t}_{tr}(0)=\overline{t}_{tr}(L)=\overline{t}_{tr}=\frac{\int_0^L\left[1+k_0\int_0^x\frac{e^{\beta U(y)}}{D(y)}dy\right]\left[1+k_Le^{-\beta\Delta U}\int_x^L\frac{e^{\beta U(y)}}{D(y)}dy\right]e^{-\beta U(x)}dx}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy}. \tag{3.7}$$

At the moment we have no simple qualitative explanation for the direction independence of the average translocation time. In the Appendix we derive a similar result for an asymmetric discrete two-site model of the channel. The analysis presented in the Appendix suggests that the direction independence of the average translocation time, $\overline{t}_{tr}(0)=\overline{t}_{tr}(L)$, is a consequence of a more general relation: namely, the direction independence of the probability density for the translocation time, $\varphi_{tr}(t|0)=\varphi_{tr}(t|L)$. We cannot prove this general relation for an arbitrary asymmetric potential and position-dependent diffusion coefficient.

In contrast to the average translocation time, the average return times are different and given by

$$\overline{t}_r(0)=\frac{\int_0^L\left[1+k_Le^{-\beta\Delta U}\int_x^L\frac{e^{\beta U(y)}}{D(y)}dy\right]^2e^{-\beta U(x)}dx}{\left[1+k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy\right]\left[k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy\right]}, \tag{3.8}$$

$$\overline{t}_r(L)=\frac{\int_0^L\left[1+k_0\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy\right]^2e^{-\beta U(x)}dx}{\left[1+k_0\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy\right]\left[k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy\right]}. \tag{3.9}$$

The average lifetimes in the channel for particles that enter through the opposite ends can be written in terms of the conditional average lifetimes and the translocation and return probabilities for particles that enter the channel at $x_0=0$ and $x_0=L$. These probabilities, denoted as $P_{tr}(0)$, $P_r(0)$, $P_{tr}(L)$, and $P_r(L)$, respectively, are related to the splitting probabilities in Eq. (2.6) by $P_{tr}(0)=P_L(0)$, $P_{tr}(L)=P_0(L)$, $P_r(0)=P_0(0)$, and $P_r(L)=P_L(L)$. Using these notations we can write [cf. Eq. (2.11)]

$$\begin{aligned}\overline{t}(0)&=\overline{t}_r(0)P_r(0)+\overline{t}_{tr}P_{tr}(0),\\ \overline{t}(L)&=\overline{t}_r(L)P_r(L)+\overline{t}_{tr}P_{tr}(L).\end{aligned} \tag{3.10}$$

The translocation and return probabilities are derived in Ref. 6. Combining the expressions in Eqs. (3.7)–(3.9) with the corresponding results from Ref. 6 [or found from Eq. (3.6)], we obtain

$$\begin{aligned}\overline{t}(0)&=\frac{\int_0^L\left[1+k_Le^{-\beta\Delta U}\int_x^L\frac{e^{\beta U(y)}}{D(y)}dy\right]e^{-\beta U(x)}dx}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy},\\ \overline{t}(L)&=\frac{\int_0^L\left[1+k_0\int_0^x\frac{e^{\beta U(y)}}{D(y)}dy\right]e^{-\beta U(x)}dx}{k_0+k_Le^{-\beta\Delta U}+k_0k_Le^{-\beta\Delta U}\int_0^L\frac{e^{\beta U(y)}}{D(y)}dy}.\end{aligned} \tag{3.11}$$

One can check that the weighted sum of these lifetimes depends only on $U(x)$ and does not depend on $D(x)$, k_0, and k_L:

$$k_0\overline{t}(0)+k_Le^{-\beta\Delta U}\overline{t}(L)=\int_0^Le^{-\beta U(x)}dx. \tag{3.12}$$

The average times in Eqs. (3.7)–(3.9) and (3.11) are the main results of this paper. They are discussed in detail in the following section.

IV. DISCUSSION

The general formulas for the average lifetimes derived above contain many parameters. To illustrate some features of the behavior of these functions we now discuss several cases in which the general formulas significantly simplify and the number of parameters decreases. We consider a symmetric case and assume that (a) $U(x)=U(L-x)$, (b) the diffusion coefficient in the channel is a constant, $D(x)=\text{const}=D_{ch}$, and (c) the rate constants k_0 and k_L are equal and are given by[10]

$$k_0=k_L=k=\frac{4D_b}{\pi a}, \tag{4.1}$$

where a is the channel radius and D_b is the particle diffusion constant in the bulk outside the membrane which in general may differ from D_{ch}. This expression for k is derived and tested against Brownian dynamics simulations in Ref. 10. According to assumption (a), $U(0)=U(L)$ and, hence, $\Delta U=0$. In the symmetric case the two average return times are equal and will be denoted by $\overline{t}_r=\overline{t}_r(0)=\overline{t}_r(L)$. The two average lifetimes are also equal and will be denoted by $\overline{t}=\overline{t}(0)=\overline{t}(L)$.

The discussion is split into three pieces. First, we consider the case of no potential. Here the main focus is on the dependence of the average lifetimes on the geometric parameters of the channel, a and L, and the diffusion constants in the channel and in the bulk. In Sec. IV B we consider the case of a square-well potential that occupies the entire channel. This means that the particle undergoes isotropic diffusion everywhere except at the channel boundaries where there is a finite bias that draws the particle into the channel. Such a potential is a caricature of the potential typical for many channels. A broad potential well is required because the translocation probability in the absence of the well is vanishingly small.[6] In this subsection we study how the average lifetimes depend on the well depth. Finally, in Sec. IV C we discuss the case of a square-well potential that occupies only part of the channel. The main focus of this subsection is on the dependence of the lifetimes on the length of the well. Surprisingly, this dependence is nonmonotonic for the average translocation time.

A. No potential well

In the simplest case, when $U(x)=0$, we have

$$\overline{t}_{tr}=\tau\frac{1+\mu+\dfrac{\mu^2}{6}}{2+\mu},\quad \overline{t}_r=\tau\frac{1+\mu+\dfrac{\mu^2}{3}}{(1+\mu)(2+\mu)},\tag{4.2}$$

where

$$\tau=\frac{L}{k}=\frac{\pi aL}{4D_b},\quad \mu=\frac{kL}{D_{ch}}=\frac{L^2}{D_{ch}\tau}=\frac{4LD_b}{\pi aD_{ch}}.\tag{4.3}$$

In the most interesting case of a long and narrow channel ($\mu\gg1$) the conditional lifetimes in Eq. (4.2) take the form

$$\overline{t}_{tr}\simeq\frac{\tau\mu}{6}=\frac{L^2}{6D_{ch}},\quad \overline{t}_r\simeq\frac{\tau}{3}=\frac{\pi aL}{12D_b}.\tag{4.4}$$

As might be expected, $\overline{t}_{tr}$ is proportional to the ratio L^2/D_{ch}. It is interesting that $\overline{t}_r$ does not depend on D_{ch} and depends only on D_b. Another interesting feature of $\overline{t}_r$ is its linear dependence on both the channel length and radius.

In the case of no potential the translocation and return probabilities are given by[6]

$$P_{tr}=\frac{1}{2+\mu},\quad P_r=\frac{1+\mu}{2+\mu}.\tag{4.5}$$

The average lifetime in this channel is

$$\overline{t}=\overline{t}_rP_r+\overline{t}_{tr}P_{tr}=\frac{\tau}{2}=\frac{\pi aL}{8D_b}.\tag{4.6}$$

It is interesting that, similar to $\overline{t}_r$, $\overline{t}$ depends only on D_b and not on D_{ch} and is proportional to the channel length and radius. It is worth mentioning that this average lifetime is different from the average lifetime of a particle uniformly distributed over the channel length, which is used to characterize thermal fluctuations of the number of particles in the channel.[10] This time depends on both D_b and D_{ch} and is equal to $(L^2/12D_{ch})(1+3\pi D_{ch}a/2D_bL)$.

It is informative to consider the ratio of the two terms on the right-hand side of Eq. (4.6):

$$\frac{\overline{t}_{tr}P_{tr}}{\overline{t}_rP_r}=\frac{1+\mu+\dfrac{\mu^2}{6}}{1+\mu+\dfrac{\mu^2}{3}}.\tag{4.7}$$

The ratio increases from 0.5 to unity as μ decreases from infinity to zero. Thus, although the times $\overline{t}_{tr}$ and $\overline{t}_r$ are quite different for long channels, $\overline{t}_{tr}\gg\overline{t}_r$, their contributions into $\overline{t}$ are comparable:

$$\overline{t}_rP_r=\frac{2}{3}\overline{t},\quad \overline{t}_{tr}P_{tr}=\frac{1}{3}\overline{t}.\tag{4.8}$$

This happens because the large time $\overline{t}_{tr}$ is multiplied by the small translocation probability while the return probability is close to unity.

B. Potential well occupies the entire channel

In this subsection, we consider a square-well potential that occupies the entire channel

$$U(x)=-U_0H(x)H(L-x),\tag{4.9}$$

where U_0 is the well depth, $U_0>0$, and $H(x)$ is the Heaviside step function. The conditional lifetimes for this case are given by

$$\overline{t}_{tr}=\tau e^{\beta U_0}\frac{1+\mu e^{-\beta U_0}+\dfrac{\mu^2}{6}e^{-2\beta U_0}}{2+\mu e^{-\beta U_0}}\tag{4.10}$$

and

$$\overline{t}_r=\tau e^{\beta U_0}\frac{1+\mu e^{-\beta U_0}+\dfrac{\mu^2}{3}e^{-2\beta U_0}}{(1+\mu e^{-\beta U_0})(2+\mu e^{-\beta U_0})}.\tag{4.11}$$

For long and narrow channels ($\mu\gg1$) with deep wells that satisfy

$$\beta U_0\gg\ln\mu,\tag{4.12}$$

these times are equal to one another and proportional to $\exp(\beta U_0)$:

$$\overline{t}_{tr}=\overline{t}_r=\frac{\tau}{2}e^{\beta U_0}=\frac{\pi aL}{8D_b}e^{\beta U_0},\tag{4.13}$$

as might be expected. Figure 2 shows how $\overline{t}_{tr}$ and $\overline{t}_r$ approach their limiting behavior in Eq. (4.13). Relaxation to quasiequilibrium in a deep potential well occurs much faster than escape. This is why the lifetimes in Eq. (4.13) are independent of D_{ch}. They depend only on D_b as the rate constant k (which determines the efficiency of the escape from the channel) is proportional to D_b.

The translocation and return probabilities for the case when the well occupies the entire channel are given by[6]

$$P_{tr}=\frac{1}{2+\mu e^{-\beta U_0}},\quad P_r=\frac{1+\mu e^{-\beta U_0}}{2+\mu e^{-\beta U_0}}.\tag{4.14}$$

Using these probabilities and the conditional lifetimes in Eqs. (4.10) and (4.11), one can find the average lifetime

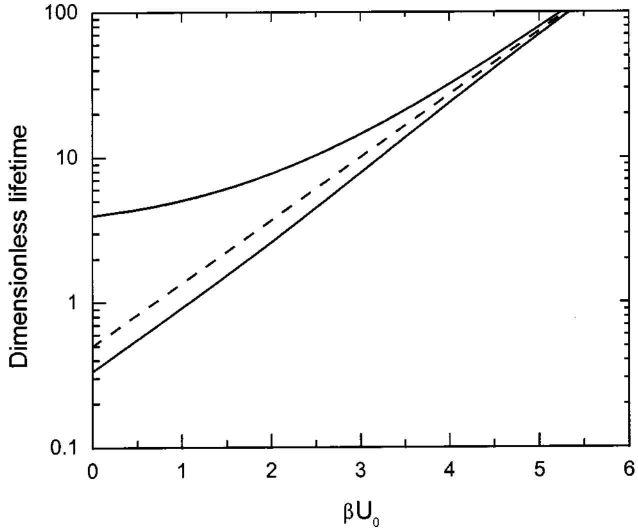

FIG. 2. Dependences $\overline{t_{tr}}/\tau$ and $\overline{t_r}/\tau$, the upper and lower solid curves, respectively, as functions of the well depth for the square-well potential occupying the entire channel at $\mu=20$. The times $\overline{t_{tr}}$ and $\overline{t_r}$ are given in Eqs. (4.10) and (4.11). The dashed curve shows the asymptotic behavior of the ratio that follows from Eq. (4.13).

$$\overline{t}=\overline{t_r}P_r+\overline{t_{tr}}P_{tr}=\frac{1}{2}\tau e^{\beta U_0}. \tag{4.15}$$

The two terms of the sum are approximately equal for deep wells, when $\beta U_0 \gg \ln \mu$. This happens because $\overline{t_r}\simeq\overline{t_{tr}}$ and $P_r\simeq P_{tr}\simeq 0.5$ in this limiting case. The ratio of these two terms considered as a function of the well depth varies from 0.5 for $U_0=0$ to unity as $\beta U_0\to\infty$.

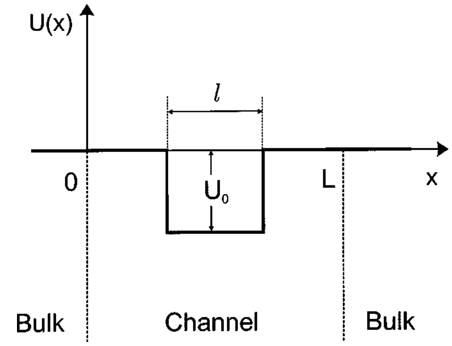

FIG. 3. Square-well potential in Eq. (4.16).

C. Potential well occupies part of the channel

In this subsection we consider a symmetric square potential well of length l that occupies the central part of the channel. In this case,

$$U(x)=-U_0H\left(x-\frac{L-l}{2}\right)H\left(\frac{L+l}{2}-x\right), \tag{4.16}$$

where U_0 is the well depth, $U_0>0$. This potential is shown in Fig. 3. The average lifetime in the channel for returning particles is given by

$$\overline{t_r}=\tau e^{\beta U_0}\frac{\mathrm{Num}_r}{[1+\mu(1-\lambda+\lambda e^{-\beta U_0})][2+\mu(1-\lambda+\lambda e^{-\beta U_0})]}, \tag{4.17}$$

where $\lambda=l/L$ is the fraction of the channel occupied by the well and

$$\begin{aligned}\mathrm{Num}_r=&\lambda+(1-\lambda)e^{-\beta U_0}+\mu[\lambda(1-\lambda)\\&+(1-2\lambda+2\lambda^2)e^{-\beta U_0}+\lambda(1-\lambda)e^{-2\beta U_0}]\\&+\frac{\mu^2}{12}[3\lambda(1-\lambda)^2+2(1-\lambda)(2-4\lambda+5\lambda^2)e^{-\beta U_0}\\&+\lambda(9-18\lambda+13\lambda^2)e^{-2\beta U_0}+6\lambda^2(1-\lambda)e^{-3\beta U_0}].\end{aligned} \tag{4.18}$$

The plots in Fig. 4 show the behavior of $\overline{t_r}$ as a function of λ for $\beta U_0=1$, 2, and 3 for $\mu=20$. As might be expected, $\overline{t_r}$ monotonically grows as λ increases.

In contrast, the average translocation time is a nonmonotonic function of λ. This time is given by

$$\overline{t_{tr}}=\tau e^{\beta U_0}\frac{\mathrm{Num}_{tr}}{2+\mu(1-\lambda+\lambda e^{\beta U_0})}, \tag{4.19}$$

where

$$\begin{aligned}\mathrm{Num}_{tr}=&\lambda+(1-\lambda)e^{-\beta U_0}+\mu[\lambda(1-\lambda)+\\&(1-2\lambda+2\lambda^2)e^{-\beta U_0}+\lambda(1-\lambda)e^{-2\beta U_0}]\\&+\frac{\mu^2}{12}[3\lambda(1-\lambda)^2+2(1-\lambda)(1-2\lambda+4\lambda^2)\\&\times e^{-\beta U_0}+\lambda(3-6\lambda+5\lambda^2)e^{-2\beta U_0}].\end{aligned} \tag{4.20}$$

The behavior of $\overline{t_{tr}}$ as a function of λ is shown in Fig. 5 for $\beta U_0=1$, 2, and 3 for $\mu=20$. One can check that in the limiting case of long and narrow channel ($\mu\gg 1$) with a deep potential well ($\beta U_0\gg\ln\mu$) the average translocation time has a maximum at $\lambda=1/2$, i.e., when the well occupies exactly one half of the channel, $l=L/2$. The time at the maximum is given by

$$\overline{t_{tr}}|_{\lambda=1/2}=\frac{\tau\mu}{16}e^{\beta U_0}. \tag{4.21}$$

The turnover behavior of $\overline{t_{tr}}$ considered as a function of λ seems rather counterintuitive and deserves some explanations. The λ dependence of the average translocation time is determined by a competition of two effects: (i) the increase

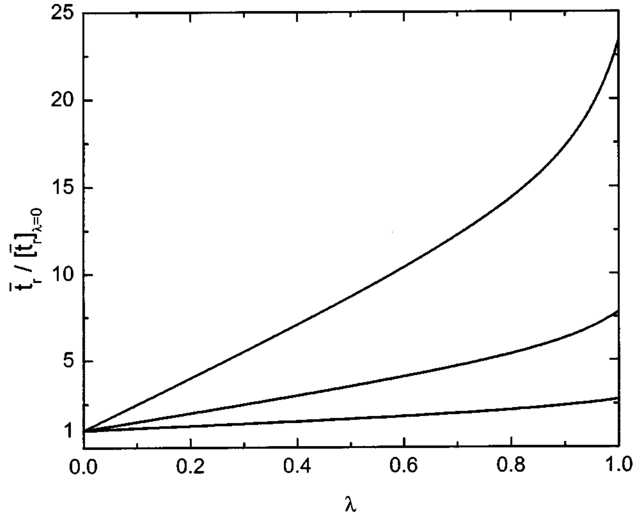

FIG. 4. Ratio of $\overline{t_r}$ in Eq. (4.17) to its value at $\lambda=0$ given in Eq. (4.2) as a function of the fraction of the channel occupied by the symmetric square potential well, λ, for $\mu=20$ and well depth $\beta U_0=1$, 2, and 3 (from bottom to top).

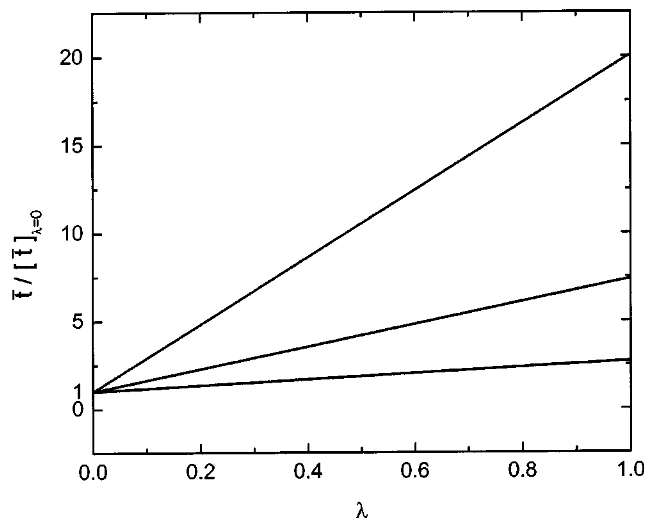

FIG. 6. Ratio of $\overline{t}$ in Eq. (4.23) to its value at $\lambda=0$ given in Eq. (4.6) as a function of λ, for $\mu=20$ and well depth $\beta U_0=1$, 2, and 3 (from bottom to top).

of the average time spent by the particle in the well with λ and (ii) the decrease in the probability for the particle that has escaped from the well to come back. The first effect is more important at small λ and leads to an increase in the average translocation time. The second effect starts to dominate as λ approaches unity, leading to a decrease in the average translocation time. Thus, when λ varies from zero to unity, the average translocation time first grows and reaches a maximum and then decreases. This is a qualitative explanation of the turnover behavior of $\overline{t_{tr}}$.

The translocation and return probabilities for the case of a square potential well that occupies the fraction λ of the channel are given by[6]

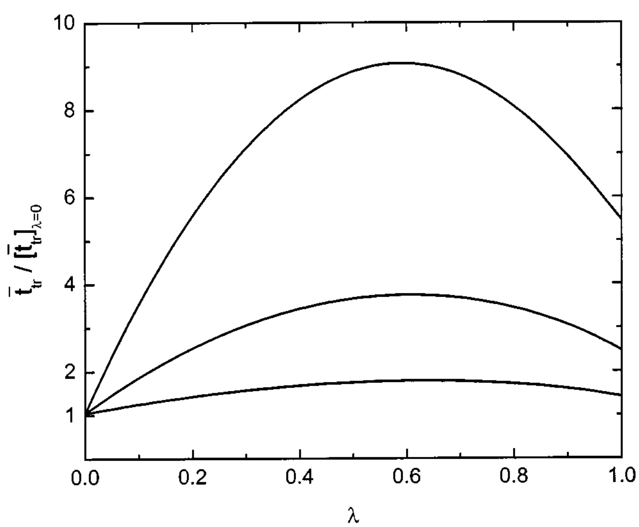

FIG. 5. Nonmonotonic dependence of the average translocation time on the fraction of the channel occupied by the well. The curves show the ratio of $\overline{t_{tr}}$ in Eq. (4.19) to its value at $\lambda=0$ given in Eq. (4.2) as a function of λ, for $\mu=20$ and well depth $\beta U_0=1$, 2, and 3 (from bottom to top).

$$P_{tr}=\frac{1}{2+\mu(1-\lambda+\lambda e^{-\beta U_0})},$$
$$P_r=\frac{1+\mu(1-\lambda+\lambda e^{-\beta U_0})}{2+\mu(1-\lambda+\lambda e^{-\beta U_0})}. \tag{4.22}$$

Using these probabilities and the conditional average lifetimes in Eqs. (4.17) and (4.19), one can find the unconditional average lifetime by

$$\overline{t}=\overline{t_r}P_r+\overline{t_{tr}}P_{tr}=\frac{\tau}{2}(1-\lambda+\lambda e^{\beta U_0}). \tag{4.23}$$

The final expression for $\overline{t}$ [as well as the results in Eqs. (4.6) and (4.15)] can be easily obtained from the relation in Eq. (3.12). The dependence of this time on λ is presented in Fig. 6, which shows that $\overline{t}$ monotonically grows as λ increases, as one might expect on the basis of general intuitive ideas.

To test our theory we performed three-dimensional Brownian dynamics simulations for the channel with the dimensionless radius $a=5.5$ and length $L=200$. We take $D_b=D_{ch}=0.5$ and the square-well potential that is symmetric about the channel center. Figures 7, 8, and 9 show the average translocation and return times as well as the average particle lifetime in the channel, $\overline{t_{tr}}$, $\overline{t_r}$, and $\overline{t}$, respectively, as functions of the well depth βU_0 for three values of well length $l=120$, 176, and 198. It is seen that theoretical predictions agree well with the simulation results.

V. CONCLUDING REMARKS

The main results of this paper are the expressions in Eqs. (3.7)–(3.9) for the average conditional lifetimes of the particle in the channel, as well as in the expressions in Eq. (3.11) for the total (unconditional) average lifetimes for particles that enter the channel from opposite sides. These expressions show how the lifetimes depend on the particle–channel interaction, which is described in terms of the

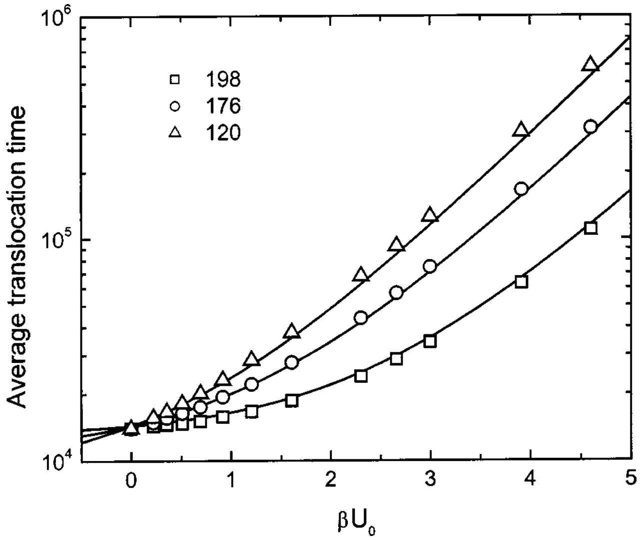

FIG. 7. Average translocation time $\overline{t_{tr}}$ as a function of the well depth for well length $l=120$, 176, and 198 (from top to bottom). The curves are drawn according to Eq. (4.19).

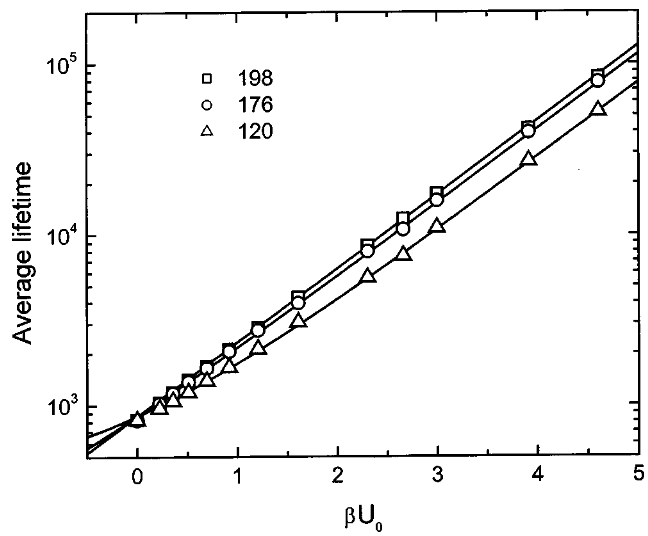

FIG. 9. Average lifetime $\overline{t}$ as a function of well depth for the same values of the well length as in Fig. 8. The curves are drawn according to Eq. (4.23).

potential of mean force, $U(x)$, and the position-dependent diffusion coefficient of the particle in the channel, $D_{ch}(x)$.

The average lifetimes are important for understanding channel functioning, especially in the case when particles cannot pass each other, so that one particle blocks the channel for the passage of others. In the simplest model this blockage makes it impossible for another particle to enter the channel until the first particle escapes. The efficiency of the channel operation (the metabolite flux facilitated by the channel) is determined by the interplay between the particle lifetime in the channel and the time between successive attempts to enter the channel made by particles in the bulk. If the former time is much larger than the latter, most of the attempts are unsuccessful because the channel is blocked most of the time. In the opposite limiting case when the particle lifetime in the channel is much smaller than the time between successive attempts, the channel is empty most of the time. It is clear that an optimal regime for channel operation is realized when the two times are close to each other.

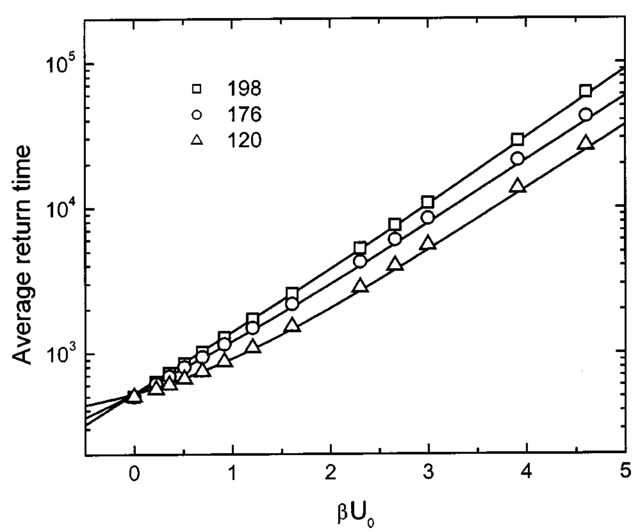

FIG. 8. Average return time $\overline{t_r}$ as a function of the well depth for well length $l=120$, 176, and 198 (from bottom to top). The curves are drawn according to Eq. (4.17). Note that the order of the curves is reversed compared to that in Fig. 7.

There is another important parameter that determines the efficiency of the channel operation: the particle translocation probability. In our previous study[6] we have shown that this probability increases with the depth of the potential well. According to Eqs. (3.11) of the present paper, the average lifetime also increases with this parameter. Thus, when the well is deep enough so that the translocation probability is close to its maximum value 0.5, the particle lifetime in the channel is large. We will address the question of optimal channel functioning in a forthcoming paper.

The theory developed above assumes that the channel dynamics is much faster than that of the particle. In reality, this is not necessarily the case. One can easily imagine that characteristic time scales associated with the particle and channel dynamics are comparable. If so, one has to treat both dynamics on an equal footing, which leads to a much more complicated multidimensional problem. This general problem reduces to our one-dimensional model by the adiabatic elimination of fast variables, which is justified on condition that the channel dynamics are fast enough.

This paper deals with neutral solutes. A similar set of questions arises in connection with the ion passage through membrane channels.[11] These questions were addressed in recent papers[12] where the Coulomb interaction of ions and charges on the channel walls was treated in the framework of the Poisson–Boltzmann approach. The analysis in Ref. 12 was based on the one-dimensional Fokker–Planck equation in phase space. We believe that our approach, which makes use of the diffusion equation, can be applied to ion permeation if the above-mentioned reduction to the one-dimensional description is justified.

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APPENDIX: PROBABILITY DENSITY OF THE TRANSLOCATION TIME FOR AN ASYMMETRIC TWO-SITE CHANNEL

The kinetic scheme representing an asymmetric two-site channel is

$$\overset{k_{1\ off}}{\longleftarrow}\ \overset{1}{\text{—}}\ \underset{k_2}{\overset{k_1}{\rightleftarrows}}\ \overset{2}{\text{—}}\ \overset{k_{2\ off}}{\longrightarrow}, \tag{A1}$$

where the rate constants k_1 and k_2 characterize transitions between the two sites of the channel, while the rate constants $k_{1\ off}$ and $k_{2\ off}$ characterize escape from the channel into the bulk on the two sides of the membrane. Consider a particle that enters the channel from the left at time $t=0$. The propagator, which is the probability to find this particle at the time t on site i, $G_{i1}(t)$, $i=1,2$, satisfies

$$\begin{aligned}\frac{\partial G_{11}(t)}{\partial t}&=-(k_{1\ off}+k_1)G_{11}(t)+k_2G_{21}(t),\\ \frac{\partial G_{21}(t)}{\partial t}&=k_1G_{11}(t)-(k_{2\ off}+k_2)G_{21}(t),\end{aligned} \tag{A2}$$

with the initial condition $G_{11}(t)=1$, $G_{21}(t)=0$. Solving this set, one can find that the Laplace transform of $G_{21}(t)$ is given by

$$\hat{G}_{21}(s)=\frac{k_1}{(s+k_{1\ off}+k_1)(s+k_{2\ off}+k_2)-k_1k_2}. \tag{A3}$$

Then one can find the Laplace transform of the translocation flux:

$$\hat{f}_{tr}(s|1)=k_{2\ off}\hat{G}_{21}(s). \tag{A4}$$

The particle translocation probability is

$$P_{tr}(1)=\hat{f}_{tr}(0|1)=k_{2\ off}\hat{G}_{21}(0). \tag{A5}$$

The Laplace transform of the probability density of the translocation time is given by

$$\begin{aligned}\hat{\varphi}_{tr}(s|1)&=\frac{\hat{f}_{tr}(s|1)}{P_{tr}(1)}=\frac{\hat{G}_{21}(s)}{\hat{G}_{21}(0)}\\ &=\frac{(k_{1\ off}+k_1)(k_{2\ off}+k_2)-k_1k_{21}}{(s+k_{1\ off}+k_1)(s+k_{2\ off}+k_2)-k_1k_2}.\end{aligned} \tag{A6}$$

The average translocation time for the particle that starts from site 1 is

$$\begin{aligned}\overline{t_{tr}}(1)&=-\left.\frac{d\hat{\varphi}_{tr}(s|1)}{ds}\right|_{s=0}\\ &=\frac{k_{1\ off}+k_1+k_{2\ off}+k_2}{(k_{1\ off}+k_1)(k_{2\ off}+k_2)-k_1k_2}.\end{aligned} \tag{A7}$$

The expression in Eq. (A6) shows that the probability density for the translocation time is direction independent, $\varphi_{tr}(t|1)=\varphi_{tr}(t|2)$. As a consequence, the average translocation time does not depend on the direction of the translocation also, $\overline{t_{tr}}(1)=\overline{t_{tr}}(2)$.

Similar but more cumbersome calculations for an asymmetric three-site channel show that the probability density of the translocation time is direction independent for this channel also.

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